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EXAMINER	
BERTAGNA, ANGELA MARIE	
ART UNIT	**PAPER NUMBER**
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/517,544	HAYASHIZAKI ET AL.	
	Examiner	Art Unit	
	Angela Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-58* is/are pending in the application.

4a) Of the above claim(s) *34-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33 and 52-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 October 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/9/05; 12/10/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-33 and 52-58 in the reply filed on August 4, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 34-51 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on August 4, 2006.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

2. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Specification

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. The embedded hyperlinks appear on pages 2, 17, 70, and 82-84 (paragraphs 5, 62, 64, 549, 690, 693, and 695-698). Removal of the "http" would correct this problem.

The disclosure is objected to because of the following informalities: Figures 4-6 and also pages 24, 28, 29, 31, 33, 43, 51, 52, 56, 63-65, 67-69, 71, 72, and 80-82 recite nucleic acid sequences greater than 10 nucleotides in length that are not identified by the appropriate SEQ ID NO. See MPEP § 2422.02.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 52 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 52 is indefinite, because it is unclear whether the 5' region of the mRNA template is extended (for example, via oligo capping) or if the newly synthesized first strand cDNA is extended.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 1-5, 8, 11, 26-28, 30, 32, 33, and 52-55 are rejected under 35 U.S.C. 102(b) as being anticipated by Kinzler et al. (US 5,695,937; cited in IDS).

Regarding claim 1, Kinzler teaches a method (see Example 1, column 9, lines 10-52) for preparing a fragment corresponding to a nucleotide sequence of a 5' end region of an mRNA, comprising:

(a) preparing a nucleic acid corresponding to a nucleotide sequence of the 5' end of an mRNA (column 9, lines 10-15, where cDNA is synthesized from mRNA)

(b) attaching at least one linker to the nucleic acid (column 9, lines 18-26)

(c) cleaving the nucleic acid with a restriction enzyme having its recognition site within the linker and its cleavage site within the nucleic acid corresponding to the 5' end of an mRNA (column 9, lines 27-30, where the linkers are cleaved with BsmFI)

(d) collecting a resulting DNA fragment corresponding to the 5' end of the mRNA (column 9, lines 30-32).

See also column 4, lines 33-41 and column 5, lines 7-11, where Kinzler teaches isolation of either 5' end regions or 3' end regions.

Regarding claims 2-4, Kinzler teaches that the fragment is 6-30 base pairs, an preferably 9-11 base pairs (column 6, lines 14-16), and further teaches specific examples of 9 base pair tags (see Table 1 in column 10). Therefore, Kinzler anticipates the instantly claimed fragment length ranges of 5-100 bp, 15-30 bp, and 10-30 base pairs.

Regarding claims 5 and 8, Kinzler teaches that the nucleic acid in step (a) is an mRNA derived from a biological sample (pancreas) (see column 9, lines 10-12).

Regarding claim 11, Kinzler teaches that step (a) in claim 1 above comprises:

(a1) synthesizing first strand cDNAs using RNA as a template to produce cDNA/RNA hybrids (column 9, lines 10-15 teach cDNA synthesis from pancreatic mRNA)

(a2) recovering a nucleic acid that corresponds to the 5' end of the mRNA from the cDNA/RNA hybrids (column 9, lines 10-17).

Regarding claim 26, Kinzler teaches sequencing the DNA fragment produced by the method of claim 1 (column 9, lines 47-52).

Regarding claim 27, Kinzler teaches that the method of claim 1 further comprises amplifying the nucleic acid corresponding to the 5' end region of the mRNA by a DNA polymerase (column 9, lines 32-35).

Regarding claim 28, Kinzler teaches use of the T4 DNA polymerase (column 9, lines 29-30). The specification does not define the term "heat-stable", and since the T4 polymerase is stable at 37°C, for example, this is a heat-stable polymerase.

Regarding claims 30 and 32, Kinzler teaches that the first strand cDNA (part of the double-stranded cDNA molecule generated by Kinzler in column 9, lines 10-15) is fractionated by physical means (column 9, lines 15-18 teach binding to streptavidin beads; column 5, lines 7-11 teach application of the method to 5' end fragments).

Regarding claim 33, Kinzler teaches a method for preparing a concatemer comprising one or more DNA fragments, comprising the step of ligating one or more fragments obtained by the method of claim 1 (column 9, lines 30-43; see also column 7, lines 5-13; column 4, lines 33-41 and column 5, lines 7-11 teach application of the method to the 5' end regions).

Regarding claim 52, Kinzler teaches extending the 5' end region of the sequence (column 9, lines 30-43, where the formation of concatemers is taught).

Regarding claims 53-55, Kinzler teaches that the method is applicable to development of diagnostic and research tools (column 13, line 16 – column 17, line 17) and also kits (column 8, lines 1-27).

7. Claims 1, 2, 5-12, 14, 16-21, 23-32, 52-56, and 58 are rejected under 35 U.S.C. 102(e) as being anticipated by Fischer et al. (US 2004/0002104 A1). This pre-grant publication obtains benefit of Provisional Application No. 60/375,782, filed on April 26, 2002.

Regarding claim 1, Fischer teaches a method (see Figure 3A and paragraphs 101-109) for preparing a fragment corresponding to a nucleotide sequence of a 5' end region of an mRNA, comprising:

(a) preparing a nucleic acid corresponding to a nucleotide sequence of the 5' end of an mRNA (Figure 3A, step 50, where first strand cDNA synthesis is performed; see paragraph 105 for further description)

(b) attaching at least one linker to the nucleic acid (Figure 3A, step 58, where the Q adaptor is ligated; see paragraph 107 for further description)

(c) cleaving the nucleic acid with a restriction enzyme having its recognition site within the linker and its cleavage site within the nucleic acid corresponding to the 5' end of an mRNA (Figure 3A, step 62; see paragraph 109 for further description)

(d) collecting a resulting DNA fragment corresponding to the 5' end of the mRNA (paragraph 109).

Regarding claim 2, Fischer teaches that examples of the Q adaptor that are 26 nt, 29 nt, and 27 nt (see SEQ ID Nos: 5, 8, and 12, respectively; see also paragraphs 87, 88, and 90). These adaptors contain an MmeI site or a BpmI recognition site at the 3'terminus. Since these enzymes cleave approximately 20 nucleotides from the recognition site, the resulting fragments

described above are 46-49 nucleotides in length. Therefore, the claimed fragment length range of 5-100 base pairs is anticipated by Fischer.

Regarding claims 5, 8, and 56, Fischer teaches that the nucleic acid in step (a) is an mRNA derived from a biological sample (see paragraphs 80 and 105).

Regarding claim 6, Fischer teaches that step (a) in claim 1 above comprises:

(a1) substituting a 5' cap structure of the mRNA with an oligonucleotide (see the alternative embodiment depicted in Figure 3C, specifically step 84; see paragraph 112 for further description)

(a2) synthesizing a first-strand cDNA using the mRNA as a template to produce a nucleic acid corresponding to the 5' end of the mRNA (Figure 3C, step 84; see paragraph 113 for further description)

Regarding claim 7, Fischer teaches a method for preparing a DNA fragment corresponding to a nucleotide sequence of a 5' end region of an mRNA, comprising:

(a) substituting a cap structure of an mRNA with an oligonucleotide (Figure 3C, step 84 and paragraph 112), wherein the oligonucleotide comprises a restriction enzyme recognition site whose cleavage site is located in the nucleic acid corresponding the 5' end of the mRNA (paragraphs 107 and 109 teach that the Q adaptor contains a Type IIS recognition site at the 3' end. This would inherently result in the cleavage site being located within the nucleic acid corresponding to the 5' end)

(b) synthesizing a first strand cDNA using the mRNA as a template (Figure 3C, step 86 and paragraph 113)

(c) synthesizing a second strand cDNA using the first cDNA as a template (Figure 3C, step 88 and paragraph 113)

(d) cleaving a resulting double-stranded cDNA with the restriction enzyme (Figure 3C, step 90 and paragraph 113)

(e) collecting a resulting cDNA fragment corresponding to the 5' end of the mRNA (paragraph 109).

Regarding claim 9, Fischer teaches that step (a) in claim 1 comprises:

(a1) synthesizing first strand cDNAs using RNA as a template to produce cDNA/RNA hybrids (Figure 3A, step 50 and paragraph 105)

(a2) selecting a particular cDNA/RNA hybrid that has the 5' cap structure of the mRNA using a selective binding substance that specifically recognizes the 5' cap structure (Figure 3A, step 54 and paragraph 106)

(a3) recovering a nucleic acid that corresponds to the 5' end of the mRNA (Figure 3A, step 54 and paragraph 106).

Regarding claim 10, Fischer teaches that the nucleic acid prepared in step a of claim 9 is a full-length cDNA (paragraphs 103-104 and 106) and that the selective binding substance is attached to a support (Figure 3A, step 54 and paragraph 106 teach streptavidin beads).

Regarding claim 11, Fischer teaches that step (a) in claim 1 above comprises:

(a1) synthesizing first strand cDNAs using RNA as a template to produce cDNA/RNA hybrids (Figure 3A, step 50 and paragraph 105)

(a2) recovering a nucleic acid that corresponds to the 5' end of the mRNA (Figure 3A, step 54 and paragraph 106).

Regarding claim 12, Fischer teaches that step (a) of claim 1 comprises:

(a1) synthesizing first strand cDNAs using RNA as a template to produce cDNA/RNA hybrids (Figure 3A, step 50 and paragraph 105)

(a2) conjugating a selective binding substance to a 5' cap structure of an mRNA present in the RNAs (Figure 3A and paragraph 105teach that biotin is attached to the mRNA prior to cDNA synthesis)

(a3) contacting the cDNA/RNA hybrids with a support, wherein another matching selective binding substance is fixed to the support, and the matching selective binding substance (Figure 3A, step 54 and paragraphs 105-106 teach binding the hybrids to streptavidin beads)

(a4) recovering the a nucleic acid corresponding to the 5' end of the mRNA from the mRNA fixed to the support (see Figure 3A and paragraphs 106-107).

Regarding claim 14, Fischer teaches that the selective binding substance is biotin and that the matching binding substance is streptavidin (Figure 3A and paragraphs 105-106).

Regarding claims 16 and 58, Fischer teaches that the support is made of magnetic streptavidin-coated beads (paragraph 183).

Regarding claim 17, Fischer teaches that step (b) of claim 1 above comprises:

(b1) attaching a linker to an end region corresponding to the nucleotide sequence of a 5' end region of the mRNA (Figure 3A, step 58, where the Q adaptor is ligated; see paragraph 107 for further description), wherein the linker contains at least one restriction enzyme recognition site for a restriction enzyme that cleaves at a site different than its recognition sequence (paragraphs 107 and 109 teach that the Q adaptor contains a Type IIS recognition site at the 3' end. This would inherently result in the cleavage site being located within the nucleic acid corresponding to the 5' end)

(b2) synthesizing a second-strand cDNA using the nucleic acid as a template (Figure 3A, step 60 and paragraph 107)

(b3) treating a resulting linker-bound double-stranded cDNA with the restriction enzyme (Figure 3A, step 62 and paragraph 109)

(b4) recovering a resulting fragment that contains a linker moiety and part of the cDNA corresponding to the 5' end region of the mRNA (paragraph 109)

Regarding claim 18, Fischer teaches that the linker contains a double-stranded oligonucleotide region and that the second-strand cDNA is synthesized using the linker (Figure 3A and paragraph 107).

Regarding claim 19, Fischer teaches that the second-strand cDNA is synthesized using other oligonucleotides that complement (at least partially) the linker (paragraph 107, 110, and 111).

Regarding claims 20 and 21, Fischer teaches that a selective binding substance (specifically, biotin) is attached to the linker, and that the recovering step comprises binding the selective binding substance to a matching binding substance on a support (streptavidin beads), and recovering the support (see Figure 3A, step 54 and paragraphs 105-106).

Regarding claims 23-25, Fischer teaches that the restriction enzyme is a Class IIS enzyme, such as GsuI, MmeI, BpmI (Figure 3A, step 62; see also paragraphs 20 and 109).

Regarding claim 26, Fischer teaches sequencing the DNA fragment produced by the method of claim 1 (paragraphs 152 and 154).

Regarding claims 27-29, Fischer teaches that the method of claim 1 further comprises amplifying the nucleic acid corresponding to the 5' end region of the mRNA by a DNA polymerases, specifically the heat-stable Pfu polymerase (paragraphs 126 and 190-191).

Regarding claims 30 and 32, Fischer teaches that the first strand cDNA is synthesized and fractionated by physical means (Figure 3A, step 54 and paragraphs 105-106 teach fractionation using streptavidin beads.

Regarding claim 31, Fischer teaches that the nucleic acid is fractionated by hybridizing to a plurality of nucleic acids (paragraph 117).

Regarding claim 52, Fischer teaches extending the 5' end region of the sequence (Figure 3C and paragraph 112 teach extension of the 5' end of the mRNA template via ligation of the Q adaptor; paragraph 107 teaches extension (tailing) of the 5' end of the first strand cDNA molecule).

Regarding claims 53-55, Fischer teaches that the method is applicable to development of diagnostic and research tools (paragraphs 44-47).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 6, 9, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kinzler et al. (US 5,695,937; cited on IDS) in view of Maruyama et al. (Gene (1994) 138: 171-174; cited on IDS).

Kinzler teaches the method of claims 1 and 30, as discussed above.

Kinzler teaches that the 5' cap of the newly synthesized cDNA can be utilized for labeling or binding a capture means for isolation of a 5' defined nucleotide sequence tag (column

5, lines 7-11). However, Kinzler does not teach substitution of the 5' mRNA cap with an oligonucleotide.

Maruyama teaches a method for isolating full-length cDNA transcripts comprising substitution of the 5' cap structure in the mRNA template with an oligonucleotide (see abstract and Figure 1). Maruyama teaches that the method is a rapid and simple way to isolate the 5' end of a cDNA transcript (see abstract and page 171, column 2 – page 172, column 1; see also page 174, column 1).

Regarding claim 6, Maruyama teaches: (a) substitution of the 5' cap in an mRNA template with an oligonucleotide and (b) synthesizing a first strand cDNA using the mRNA as a template to produce a second nucleic acid corresponding to the 5' end of the mRNA (see Figure 1 and page 172).

Regarding claim 9, Maruyama teaches synthesizing first strand cDNAs using RNA as a template and producing cDNA/RNA hybrids of the resulting first-strand cDNAs and the RNAs (page 172, column 1-2, the RT step), selecting a particular cDNA/RNA hybrid that has the 5' cap structure of the mRNA using a selective binding substance which specifically recognizes the 5' cap structure (the PCR step on page 172 and Figure 1 uses a primer specific to the substituted oligonucleotide), and recovering a nucleic acid corresponding to the 5' end of the mRNA (see Figure 2, where agarose gel electrophoresis is used to recover the nucleic acid).

Regarding claim 31, Maruyama teaches that the nucleic acid is fractionated by hybridization to a plurality of nucleic acid (the PCR step on page 172 utilizes a plurality of nucleic acid primers that hybridize to the target. Following amplification the products are fractionated in an agarose gel).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to utilize oligo capping as taught by Maruyama in the method of Kinzler. One application of the Kinzler method was to generate sequence tags from the 5' end region of a cDNA transcribed from an mRNA sample (column 4, lines 33-41 and column 5, lines 7-11). Since Maruyama taught that conventional reverse transcription protocols often generate a high percentage of truncated products (page 171) and further taught a rapid and simple method for selecting full-length transcripts (see abstract and page 172 cited above), the ordinary practitioner would have been motivated to perform the oligo-capping procedure taught by Maruyama prior to first-strand cDNA synthesis in order to increase the number of full-length cDNAs in the resulting pool, and thereby improve the ability to generate 5' end-specific sequence tags using the method of Kinzler. This improved generation of 5' end-specific sequence tags would have improved the ability of the Kinzler method to identify novel sequences in the 5' region of an mRNA sample.

10. Claims 9, 10, 12, 14-16, and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kinzler et al. (US 5,695,937; cited on IDS) in view of Carninci et al. (Genomics (1996) 37: 327-336).

Kinzler teaches the method of claims 1 and 30, as discussed above.

Regarding claims 14-16 and 58, Kinzler teaches that the cDNA may be labeled with selective binding substances such as biotin and digoxigenin for capture by the matching binding substances streptavidin and digoxigenin, respectively (column 5, lines 7-11). Kinzler also teaches the use of magnetic streptavidin-coated beads for capture (column 9, lines 15-18).

Kinzler teaches that the 5' cap of the newly synthesized cDNA can be utilized for labeling or binding a capture means for isolation of a 5' defined nucleotide sequence tag (column 5, lines 7-11). However, Kinzler does not teach conjugation of a selective binding agent to the 5' cap of the mRNA.

Carninci teaches a high efficiency method ("CAP trapper") for isolating full-length cDNA molecules (see Figure 1 and pages 328-329).

Regarding claim 9, the method of Carninci comprises synthesizing first strand cDNAs using RNA as a template and producing cDNA/RNA hybrids of the resulting first-strand cDNAs and the RNAs (page 328, column 1 "First-strand cDNA preparation" and Figure 1), selecting a particular cDNA/RNA hybrid that has the 5' cap structure of the mRNA using a selective binding substance which specifically recognizes the 5' cap structure (page 328 "Blocking of magnetic beads and capturing the nucleic acids" and Figure 1, where biotin conjugated to the 5' cap structure of the mRNA is bound to streptavidin beads), and recovering a nucleic acid corresponding to the 5' end of the mRNA (page 328, "Blocking of magnetic beads and capturing the nucleic acids" and Figure 1).

Regarding claim 10, Carninci teaches preparation of a full-length cDNA using the method described above (page 328, column 2; see also abstract). Carninci further teaches that the selective binding substance is attached to a support (page 328, column 2, where the selective binding substance is magnetic beads coated with streptavidin).

Regarding claim 12, the method of Carninci comprises:

(a) synthesizing first strand cDNAs using RNA as a template to produce cDNA/RNA hybrids (page 328, column 1 "First-strand cDNA preparation" and Figure 1)

(b) conjugating a selective binding substance to a 5' cap structure of an mRNA present in the RNAs (page 328, column 2, "Biotinylation of diol groups of RNA"; see also Figure 1)

(c) contacting the cDNA/RNA hybrids with a support, wherein another matching selective binding substance is fixed to the support, and the matching selective binding substance (page 328 "Blocking of magnetic beads and capturing the nucleic acids" and Figure 1, where biotin conjugated to the 5' cap structure of the mRNA is bound to streptavidin-coated magnetic beads)

(d) recovering the a nucleic acid corresponding to the 5' end of the mRNA from the mRNA fixed to the support (page 328 "Blocking of magnetic beads and capturing the nucleic acids" and Figure 1, where biotin conjugated to the 5' cap structure of the mRNA is bound to streptavidin beads).

Regarding claims 14, 16, and 58, Carninci teaches that the selective binding substance is biotin and that the matching binding substance is streptavidin. Carninci further teaches that the streptavidin is coated on magnetic beads (page 328 "Blocking of magnetic beads and capturing the nucleic acids" and Figure 1).

Carninci teaches, "The overall efficiency and yield of the full-length cDNA is thus far superior to other conventional methods for the preparation of full-length cDNA libraries. Our method allows the preparation of high-content full-length cDNA libraries, even from relatively

small quantities of tissues or early embryos, with no bias in representation since no PCR amplification step has been introduced (page 328, column 1)."

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to utilize the CAP trapper method taught by Carninci in the method of Kinzler. One application of the Kinzler method was to generate sequence tags from the 5' end region of a cDNA transcribed from an mRNA sample (column 4, lines 33-41 and column 5, lines 7-11). Since Carninci taught that conventional reverse transcription protocols often generate a high percentage of truncated products (page 327) and further taught an extremely efficient, high-yield method for selecting full-length transcripts (see page 328 cited above), the ordinary practitioner would have been motivated to attach a biotin molecule to the mRNA template as suggested by Carninici prior to first-strand cDNA synthesis in order to increase the number of full-length cDNAs in the resulting pool, and thereby improve the ability to generate 5' end-specific sequence tags using the method of Kinzler. Increasing the number of full-length cDNA molecules in the pool prior to restriction enzyme digestion and generation of tags would have improved the Kinzler method by increasing its ability to identify novel sequences in the 5' region of an mRNA sample. Finally, since Kinzler expressly taught use of the 5' cap structure for capture of 5' end regions (see column 5, lines 7-11), the ordinary practitioner could have expected a reasonable level of success in incorporating the CAP trapping procedure of Carninci for selection of full-length cDNA molecules. Therefore, the ordinary practitioner of the method taught by Kinzler, interested in improving the method's ability to generate 5' end-specific sequence tags, would have been motivated to selectively isolate full-length cDNA transcripts using the CAP trapper method of Carninci, thus resulting in the instantly claimed methods.

11. Claims 13 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kinzler et al. (US 5,695,937; cited on IDS) in view of Carninci et al. (Genomics (1996) 37: 327-336) and further in view of Edery et al. (Molecular and Cellular Biology (1995) 15(6): 3363-3371; cited on IDS) and further in view of Das et al. (Physiological Genomics (2001) 6: 57-80).

The combined teachings of Kinzler and Carninci result in the method of claims 9 and 10, as discussed above.

Neither Kinzler nor Carninci teaches that the selective binding substance is a cap-binding protein or a cap-binding antibody.

Edery teaches a method ("CAPture") of isolating full-length cDNA transcripts based on affinity capture using the cap-binding protein eIF-4e (see abstract). The method of Edery comprises the following steps: reverse transcription of mRNA to generate a cDNA/RNA hybrid, RNase A treatment, binding of eIF-4e to the 5' cap structure of the mRNA to selectively bind full-length RNA/cDNA hybrids, and binding of the eIF-4e/RNA/cDNA complex to anti-eIF-4e conjugated to sepharose beads (see Methods section, page 3364, column 2 – page 365, column 1).

Das presents a review of methods for obtaining full-length cDNA molecules. Das compared affinity selection methods taught by Carninci (cap trapper) and Edery (affinity selection using the cap-binding protein eIF-4e) and reported that the Carninci method was not specific. Specifically, Das stated, "...if we compare the ability of cap trapper to discriminate between cDNA duplex with capped mRNA (generated in vitro) or duplexed with uncapped mRNA (generated in vitro), then we are unable to obtain specific selection of capped over uncapped transcripts (J. Pelletier, data not shown). This is likely due to the fact that biotin-

hydrazide can also react with unoxidized RNA due to incipient reaction of cytosine residues. Hence, addition of biotin is not solely directed toward the cap structure. Also, it is important to note that the oxidation reaction with $NaIO_4$ is difficult to control, and the molar ratio of periodate to substrate is important, otherwise one gets destruction of base rings (page 73)."

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to substitute the affinity selection method of Edery for the cap trapper method taught by Carninci in the method resulting from the combined teachings of Carninci and Edery. Edery taught a method for isolating full-length cDNA molecules comprising affinity purification using the cap-binding protein eIF-4e (see above). Since Das taught that this method was more specific than the cap trapper method taught by Carninci and also did not involve the use of the potentially RNA-degrading reagent NaIO4 (see above), the ordinary practitioner would have been motivated to substitute the affinity purification method taught by Edery in the method of Kinzler in order to more specifically isolate full-length cDNA prior to generating 5' end region-specific tags. As discussed in greater detail in sections 10 and 11 above, the ordinary practitioner would have been motivated to isolate full-length cDNA prior to generating the 5' end region tags in order to increase the diversity of the sequence tags generated from the 5' region. Therefore, the ordinary practitioner of the method of Kinzler, interested in obtaining a highly specific method of isolating full-length cDNA molecules with minimal degradation of the mRNA template, would have been motivated to utilize the affinity purification method of Ederly, as suggested by Das, thus resulting in the instantly claimed methods.

Conclusion

No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is (571) 272-8291. The examiner can normally be reached on M-F 7:30-5 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Angela Bertagna
Examiner, Art Unit 1637
September 15, 2006

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PRIMARY EXAMINER
9/17/06